

**DOCKET NO.: ISIS0002-102 (ISIS-4313)****PATENT****In the Claims:**

This listing of claims will replace all prior versions, and listings, of claims in the application.

Please amend claims 78-81, 93-102, and 106 as indicated below.

Please add new claims 117-181 as indicated below.

1-77. (Cancelled).

78. (Currently amended) A ~~double-stranded RNA-substrate~~ composition comprising a duplex of a first oligonucleotide and a second oligonucleotide, wherein said first and said second oligonucleotides are not covalently linked, wherein each of said first and second oligonucleotides have a central portion having at least four consecutive ribofuranosyl residues having phosphodiester linkages, wherein said central portions are base-paired with each other in said duplex; at least one of said first and said second oligonucleotides having portions flanking said central portions having chemical modifications which make them resistant to single-stranded nucleases, and wherein each of said first and said second oligonucleotides comprises from eight to fifty nucleoside subunits.

79. (Currently amended) A ~~double-stranded RNA-substrate~~ composition comprising a duplex of a first oligonucleotide and a second oligonucleotide, wherein said first and said second oligonucleotides are not covalently linked, wherein each of said first and second oligonucleotides have a central portion having at least four consecutive ribofuranosyl residues having phosphodiester linkages, wherein said central portions are base-paired with each other in said duplex; at least one of said first and said second oligonucleotides having portions flanking said central portions having chemical modifications which make them resistant to single-stranded nucleases and increase their affinity for the other oligonucleotide of the duplex.

80. (Currently amended) The ~~double-stranded RNA-substrate~~ composition of claim 78, wherein said chemical modifications are phosphorothioate linkages or 2'-methoxy modifications.

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81. (Currently amended) An affinity matrix comprising the ~~double-stranded RNA substrate~~ composition of claim 78.

82-92. (Cancelled).

93. (Currently amended) A ~~double-stranded RNA substrate~~ composition of claim 78, wherein one of said oligonucleotides has the nucleotide sequence of SEQ ID NO:8.

94. (Currently amended) A ~~double-stranded RNA substrate~~ composition comprising a duplex of a first oligonucleotide and a second oligonucleotide wherein said first and said second oligonucleotides are not covalently linked, wherein each of said first and second oligonucleotides include a portion having at least four consecutive ribofuranosyl residues having phosphodiester linkages and wherein said portions are base-paired with each other in said duplex, and wherein each of said first and said second oligonucleotides comprises from eight to fifty nucleoside subunits.

95. (Currently amended) A ~~double-stranded RNA substrate~~ composition comprising a duplex of a first oligonucleotide and a second oligonucleotide wherein said first and said second oligonucleotides are not covalently linked, wherein each of said first and second oligonucleotides include a portion having at least four consecutive ribofuranosyl residues that are base-paired with each other in said duplex; and at least one of said first and said second oligonucleotides including a chemical modification that makes said oligonucleotide resistant to single-stranded nucleases, and wherein each of said first and said second oligonucleotides comprises from eight to fifty nucleoside subunits.

96. (Currently amended) A ~~double-stranded RNA substrate~~ composition comprising a duplex of a first oligonucleotide and a second oligonucleotide wherein said first and said second oligonucleotides are not covalently linked, wherein each of said first and second oligonucleotides include a portion that is base-paired with each other in said duplex; and at least one of said first

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and said second oligonucleotides having a further portion that includes a chemical modification that increases the affinity of said oligonucleotide for the other oligonucleotide, and wherein each of said first and said second oligonucleotides comprises from eight to fifty nucleoside subunits.

97. (Currently amended) A ~~double-stranded RNA substrate~~ composition comprising a duplex of a first oligonucleotide and a second oligonucleotide wherein said first and said second oligonucleotides are not covalently linked, wherein each of said first and second oligonucleotides include a portion having at least four consecutive ribofuranosyl residues and where said portions are base paired with each other in said duplex; and at least one of said first and second oligonucleotides includes a chemical modification that makes said oligonucleotide resistant to single-stranded nucleases and that increases the affinity for said oligonucleotide for the other of said oligonucleotides.

98. (Currently amended) A ~~double-stranded RNA substrate~~ composition comprising a duplex of a first oligonucleotide and a second oligonucleotide that are not covalently linked, wherein at least one of said first and said second oligonucleotides includes a chemical modification that makes said oligonucleotide resistant to single-stranded nucleases and that increases the affinity for said oligonucleotide for the other of said oligonucleotides, and wherein each of said first and said second oligonucleotides comprises from eight to fifty nucleoside subunits.

99. (Currently amended) A ~~double-stranded RNA substrate~~ composition comprising a duplex of a first oligonucleotide and a second oligonucleotide that are not covalently linked, wherein at least one of said first and said second oligonucleotides includes a chemical modification that makes said oligonucleotide resistant to single-stranded nucleases, and wherein each of said first and said second oligonucleotides comprises from eight to fifty nucleoside subunits.

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100. (Currently amended) A ~~double-stranded RNA substrate~~ composition comprising a duplex of a first oligonucleotide and a second oligonucleotide that are not covalently linked, wherein at least one of said first and said second oligonucleotides includes a chemical modification that increases the affinity for said oligonucleotide for the other of said oligonucleotides, and wherein each of said first and said second oligonucleotides comprises from eight to fifty nucleoside subunits.

101. (Currently amended) A ~~double-stranded RNA substrate~~ composition comprising a duplex of a first oligonucleotide and a second oligonucleotide, wherein said first and said second oligonucleotides are not covalently linked, wherein each of said first and second oligonucleotides include a portion having at least four consecutive ribofuranosyl residues having phosphodiester linkages, wherein said portions are base-paired with each other in said duplex, and wherein ~~one~~ each of said first and said second oligonucleotides comprises from eight to fifty nucleoside subunits.

102. (Currently amended) The ~~double-stranded RNA substrate~~ composition of claim 101 wherein said one of said first and said second oligonucleotides comprises from twelve to thirty subunits.

103-105. (Cancelled)

106. (Currently amended) A ~~double-stranded RNA substrate~~ composition comprising a duplex of a first oligonucleotide and a second oligonucleotide, wherein said first and said second oligonucleotides have a central portion having at least four consecutive ribofuranosyl residues having phosphodiester linkages, wherein said central portions are base-paired with each other in said duplex; at least one of said first and said second oligonucleotides having portions flanking said central portions, said portions having chemical modifications which make them resistant to single-stranded nucleases, and wherein one of said oligonucleotides has the nucleotide sequence of SEQ ID NO:8.

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107-116. (Cancelled).

117. (new) The composition of claim 78 wherein said chemical modifications are phosphorothioate linkages.

118. (new) The composition of claim 78 wherein said chemical modifications are 2'-methoxy modifications.

119. (new) The composition of claim 78 wherein said chemical modifications are 2'-fluoro modifications.

120. (new) The composition of claim 78 wherein said chemical modifications are 2'-O-methoxyethoxy modifications.

121. (new) The composition of claim 78 wherein one of said first and said second oligonucleotides comprises from twelve to thirty nucleoside subunits.

122. (new) The composition of claim 78 wherein one of said first and said second oligonucleotides comprises from fifteen to twenty-five nucleoside subunits.

123. (new) The composition of claim 79 wherein said chemical modifications are phosphorothioate linkages.

124. (new) The composition of claim 79 wherein said chemical modifications are 2'-methoxy modifications.

125. (new) The composition of claim 79 wherein said chemical modifications are 2'-fluoro modifications.

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126. (new) The composition of claim 79 wherein said chemical modifications are 2'-O-methoxyethoxy modifications.

127. (new) The composition of claim 79 wherein one of said first and said second oligonucleotides comprises from twelve to thirty nucleoside subunits.

128. (new) The composition of claim 79 wherein one of said first and said second oligonucleotides comprises from fifteen to twenty-five nucleoside subunits.

129. (new) The composition of claim 94 wherein said chemical modifications are phosphorothioate linkages.

130. (new) The composition of claim 94 wherein said chemical modifications are 2'-methoxy modifications.

131. (new) The composition of claim 94 wherein said chemical modifications are 2'-fluoro modifications.

132. (new) The composition of claim 94 wherein said chemical modifications are 2'-O-methoxyethoxy modifications.

133. (new) The composition of claim 94 wherein one of said first and said second oligonucleotides comprises from twelve to thirty nucleoside subunits.

134. (new) The composition of claim 94 wherein one of said first and said second oligonucleotides comprises from fifteen to twenty-five nucleoside subunits.

135. (new) The composition of claim 95 wherein said chemical modifications are phosphorothioate linkages.

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136. (new) The composition of claim 95 wherein said chemical modifications are 2'-methoxy modifications.
137. (new) The composition of claim 95 wherein said chemical modifications are 2'-fluoro modifications.
138. (new) The composition of claim 95 wherein said chemical modifications are 2'-O-methoxyethoxy modifications.
139. (new) The composition of claim 95 wherein one of said first and said second oligonucleotides comprises from twelve to thirty nucleoside subunits.
140. (new) The composition of claim 95 wherein one of said first and said second oligonucleotides comprises from fifteen to twenty-five nucleoside subunits.
141. (new) The composition of claim 96 wherein said chemical modifications are phosphorothioate linkages.
142. (new) The composition of claim 96 wherein said chemical modifications are 2'-methoxy modifications.
143. (new) The composition of claim 96 wherein said chemical modifications are 2'-fluoro modifications.
144. (new) The composition of claim 96 wherein said chemical modifications are 2'-O-methoxyethoxy modifications.
145. (new) The composition of claim 96 wherein one of said first and said second oligonucleotides comprises from twelve to thirty nucleoside subunits.

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146. (new) The composition of claim 96 wherein one of said first and said second oligonucleotides comprises from fifteen to twenty-five nucleoside subunits.

147. (new) The composition of claim 97 wherein said chemical modifications are phosphorothioate linkages.

148. (new) The composition of claim 97 wherein said chemical modifications are 2'-methoxy modifications.

149. (new) The composition of claim 97 wherein said chemical modifications are 2'-fluoro modifications.

150. (new) The composition of claim 97 wherein said chemical modifications are 2'-O-methoxyethoxy modifications.

151. (new) The composition of claim 97 wherein one of said first and said second oligonucleotides comprises from twelve to thirty nucleoside subunits.

152. (new) The composition of claim 97 wherein one of said first and said second oligonucleotides comprises from fifteen to twenty-five nucleoside subunits.

153. (new) The composition of claim 98 wherein said chemical modifications are phosphorothioate linkages.

154. (new) The composition of claim 98 wherein said chemical modifications are 2'-methoxy modifications.

155. (new) The composition of claim 98 wherein said chemical modifications are 2'-fluoro modifications.

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156. (new) The composition of claim 98 wherein said chemical modifications are 2'-O-methoxyethoxy modifications.

157. (new) The composition of claim 98 wherein one of said first and said second oligonucleotides comprises from twelve to thirty nucleoside subunits.

158. (new) The composition of claim 98 wherein one of said first and said second oligonucleotides comprises from fifteen to twenty-five nucleoside subunits.

159. (new) The composition of claim 99 wherein said chemical modifications are phosphorothioate linkages.

160. (new) The composition of claim 99 wherein said chemical modifications are 2'-methoxy modifications.

161. (new) The composition of claim 99 wherein said chemical modifications are 2'-fluoro modifications.

162. (new) The composition of claim 99 wherein said chemical modifications are 2'-O-methoxyethoxy modifications.

163. (new) The composition of claim 99 wherein one of said first and said second oligonucleotides comprises from twelve to thirty nucleoside subunits.

164. (new) The composition of claim 99 wherein one of said first and said second oligonucleotides comprises from fifteen to twenty-five nucleoside subunits.

165. (new) The composition of claim 100 wherein said chemical modifications are phosphorothioate linkages.

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166. (new) The composition of claim 100 wherein said chemical modifications are 2'-methoxy modifications.

167. (new) The composition of claim 100 wherein said chemical modifications are 2'-fluoro modifications.

168. (new) The composition of claim 100 wherein said chemical modifications are 2'-O-methoxyethoxy modifications.

169. (new) The composition of claim 100 wherein one of said first and said second oligonucleotides comprises from twelve to thirty nucleoside subunits.

170. (new) The composition of claim 100 wherein one of said first and said second oligonucleotides comprises from fifteen to twenty-five nucleoside subunits.

171. (new) The composition of claim 101 wherein said chemical modifications are phosphorothioate linkages.

172. (new) The composition of claim 101 wherein said chemical modifications are 2'-methoxy modifications.

173. (new) The composition of claim 101 wherein said chemical modifications are 2'-fluoro modifications.

174. (new) The composition of claim 101 wherein said chemical modifications are 2'-O-methoxyethoxy modifications.

175. (new) The composition of claim 101 wherein one of said first and said second oligonucleotides comprises from fifteen to twenty-five nucleoside subunits.

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176. (new) The composition of claim 106 wherein said chemical modifications are phosphorothioate linkages.

177. (new) The composition of claim 106 wherein said chemical modifications are 2'-methoxy modifications.

178. (new) The composition of claim 106 wherein said chemical modifications are 2'-fluoro modifications.

179. (new) The composition of claim 106 wherein said chemical modifications are 2'-O-methoxyethoxy modifications.

180. (new) The composition of claim 106 wherein one of said first and said second oligonucleotides comprises from twelve to thirty nucleoside subunits.

181. (new) The composition of claim 106 wherein one of said first and said second oligonucleotides comprises from fifteen to twenty-five nucleoside subunits.